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The Impact of Modifying Empirical Antibiotic Therapy Based on Intestinal Colonization Status on Clinical Outcomes of Febrile Neutropenic Patients

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ABSTRACT

Background: This paper aimed to inspect factors affecting febrile neutropenia patients with hematologic malignancies. The intestinal colonization rate of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) and carbapenem-resistant *Enterobacteriaceae* (CRE) was assessed. The rate of subsequent ESBL-E and CRE bacteremia correlated with corresponding bacterial colonization was evaluated. Further, the risk factors for ESBL-E and CRE intestinal colonization were examined. Finally, the impact of rectal swab screening combined with adapted empirical antibiotic therapy on the mortality rate of patients with febrile neutropenia was assessed.

Materials and Methods: Febrile neutropenia patients underwent rectal swabs and collection of blood culture specimens upon admission. Empirical treatment was subsequently modified according to rectal swab results if necessary. Bacteremia patients were treated according to blood culture results. Explorative forward-stepwise logistic regression analyses were used to identify risk factors for ESBL-E and CRE fecal carriage and mortality.

Results: In total, 201 rectal swabs and 402 blood samples were collected from 163 patients during 201 febrile neutropenia episodes. Of these episodes, 38 (18.90%) were colonized with ESBL-E and 30 (14.92%) with CRE. Bloodstream infections developed in 29/201 (14.42%) episodes. Only bacteremia episodes caused by Gram-negative bacilli were included in our analysis. The development of Gram-negative-rod bacteremia was observed in eight out of 38 (21.05%) ESBL-E colonized episodes and four out of 30 (13.33%) CRE-colonized episodes. A BSI developed in three out of 38 (7.89%) ESBL-E colonized episodes, and two out of 30 (6.66%) CRE-colonized episodes developed BSI with the respective organism. Multivariate analysis identified previous quinolone use as the only independent risk factor for fecal colonization of multi-drug-resistant (MDR) *Enterobacteriaceae* (ESBL-E and CRE) (odds ratio, 17.09; 95% confidence interval, 5.29 - 55.18; *P* <0.0001). No significant association was observed between ESBL-E and CRE carriage and increased risk of developing subsequent bacteremia. No significant differences were detected between groups receiving modified
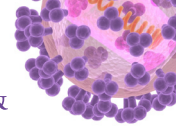
and non-modified treatments in duration of hospitalization or antibiotic therapy (univariate analysis) and 28-day mortality rate (logistic regression).
Conclusion: Quinolone exposure was a major risk factor for ESBL-E and CRE fecal carriage. Performing rectal swab screening for MDR *Enterobacteriaceae* and modifying empirical antibiotic therapy accordingly did not improve clinical outcomes of febrile neutropenia patients.

Keywords: Febrile neutropenia; Intestinal colonization; Modifying empirical therapy

INTRODUCTION

Bloodstream infections (BSIs) remain the leading cause of mortality in patients with chemotherapy-induced neutropenia [1]. Bacterial penetration of mucosal abrasions or mucositis induced by chemotherapy in the mucosal barrier during neutropenia can cause BSIs [2]. Bacterial colonization is considered the initial step in infection development, followed by translocation of colonizing bacteria. Recurring hospitalization is a major risk factor for colonization by multi-drug-resistant (MDR) bacteria in the gut. Therefore, febrile neutropenia patients are considered a high-risk population due to their repetitive hospital admissions and administration of chemotherapy. This can lead to colonization by MDR bacteria and subsequent BSI development [2]. A prospective observational multicenter study in Italy that investigated carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) BSI development in CR-KP rectal carriers reported that chemotherapy was an independent risk factor for CR-KP BSI development [3]. Furthermore, a higher BSI rate has been reported in colonized patients (50%) than in uncolonized patients (7.5%) [4]. Notably, the risk of infection is 38-fold higher in patients colonized by MDR pathogens than in non-colonized patients [5]. Moreover, a risk factor for infection and an indication to modify empirical antibiotic therapy is colonization by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella* producing carbapenemase (KPC)[6]. Furthermore, MDR pathogens are considered one of the most significant threats to the successful treatment of infection. Understanding bacterial colonization may facilitate the production of an empirical regimen with improved therapeutic effects and minimize unfavorable outcomes [5]. Colonization by bacteria in the gut influences empirical antibiotic selection in febrile neutropenia patients. Hence, early colonization status-based empirical antibiotic treatment may reduce ESBL-E BSI-related mortality by preventing lethal outcomes [7].

Narimatsub et al. demonstrated that screening for *Pseudomonas aeruginosa* colonization was predictive of the development of BSI after reduced-intensity cord blood transplantation [4]. In this study, 50% of colonized versus 7.5% of non-colonized patients developed *P. aeruginosa* BSI. Demiraslan et al. identified a significantly higher rate of bacteremia (33.3%) among patients colonized by carbapenem-resistant Gram-negative bacilli (CRGNB). In contrast, non CRGNB-colonized patients exhibited a lower bacteremia rate (9.1%) (*P* = 0.001) [8]. This highlights the importance of colonization by MDR bacteria prior to BSI development. However, no significant difference in mortality was noted between patients administered colistin and those who were not (*P* = 0.56).

Menzo et al. proposed a diagnostic and therapeutic algorithm to reduce BSI rates in neutropenic patients based on rectal swab cultures in order to identify patients infected

with *Klebisella pneumoniae* carbapenemase (KPC) producing-bacteria. The authors suggested modifying the therapeutic regimen according to the rectal swab results [9]. Notably, this paper did not cite any evidence explaining the extent to which colonizing pathogens cause bacteremia, nor the effect of the adapted treatment on patient outcomes.

Our study was conducted in Syria, a country with a poor health system and high rate of antimicrobial resistance. Estimates of ESBL-E carriage in Syria range from 26 to 66% [10, 11]. Carbapenem-resistant *Enterobacteriaceae* (CRE) producer Syrian carriages vary between centers and range from 17 to 37% [11, 12]. At centers with high rates of colonization by MDR bacteria, it has been proposed that fecal screening in combination with consecutive adaption of empirical treatment may be useful in colonized patients [7]; however, this approach has not been formally assessed. Moreover, the implementation of rectal swab surveillance as a component of standard-of-care is solely based on expert opinion. Most febrile neutropenia patients in our centers received carbapenems or colistin as a component of empirical therapy when they had been identified to be hospitalized or had previous febrile neutropenia episodes. This practice increased the administration of carbapenems and colistin, thereby increasing selection pressure.

We conducted a prospective multicenter study to assess the intestinal colonization rate of ESBL-E and CRE. This was performed for multiple reasons. First, we aimed to delineate the clinical impact of colonization by MDR bacteria in patients affected by hematological diseases. Second, we aimed to better understand the risk factors associated with rectal colonization by MDR bacteria and subsequent BSIs in order to facilitate early recognition and reduce population mortality. Third, we aimed to evaluate the rate of subsequent ESBL-E and CRE bacteremia correlated with corresponding bacterial colonization. Fourth, we aimed to identify risk factors for ESBL-E and CRE intestinal colonization. Finally, we aimed to assess the impact of rectal swab screening in combination with adapted empirical antibiotic therapy on the mortality rate of patients with febrile neutropenia.

MATERIALS AND METHODS

1. Setting, patients, and study design

All febrile neutropenia patients who received active chemotherapy treatment and provided informed consent were enrolled in this study. The patients were admitted to the infectious disease and hematology wards in two Damascus University-affiliated hospitals. This study was designed as an observational prospective multicenter cohort study and was conducted between February 1, 2018, and June 18, 2020. All subjects provided written informed consent. The study protocol was approved by the independent Ethical Review Committee of the Faculty of Medicine at Damascus University (IER no. 2018-01-011-025).

The cohort comprised adults older than 18 years of age with hematological malignancies who received chemotherapy and developed febrile neutropenia. We excluded patients who were not actively receiving chemotherapy or those who underwent total body irradiation and/or a major surgery within 1 month of admission. The same patient could be included more than once for different febrile neutropenia episodes. Information regarding baseline characteristics, clinical data, empirical antibiotic therapy, and clinical outcomes were documented. Surveillance culture results prior to first admission were not required. A rectal swab and two 15-mL specimens of blood culture, separated by 30 minutes, were obtained

from all included patients at admission. A new rectal swab was obtained in cases of febrile neutropenia episode recurrence.

All patients were treated empirically prior to obtaining rectal culture results according to the local institutional guidelines (standard-of-care) with ceftazidime, cefepime, or piperacillin/tazobactam with an antipseudomonal aminoglycoside for the first 48 hours. Results from rectal swabs and blood cultures were obtained within 48 and 120 hours, respectively. An adapted empirical antibiotic therapy as defined by institutional guidelines was used based on rectal swab results. Additionally, escalated or deescalated antibiotic treatment was applied according to blood culture results if no other infection was detected (**Fig. 1**). Rectal swabs and blood specimens were processed at the local laboratories of the two Damascus University-affiliated hospitals. Chromogenic agar media such as CHROMID® ESBL and CHROMID® CARBA (both obtained from bioMérieux Deutschland GmbH, Nürtingen, Germany) and nonchromogenic, nonselective media were used to detect bacteria in rectal swabs. Species identification and susceptibility testing were performed according to the standards set by the Clinical Laboratory and Standards Institute (CLSI) using Becton
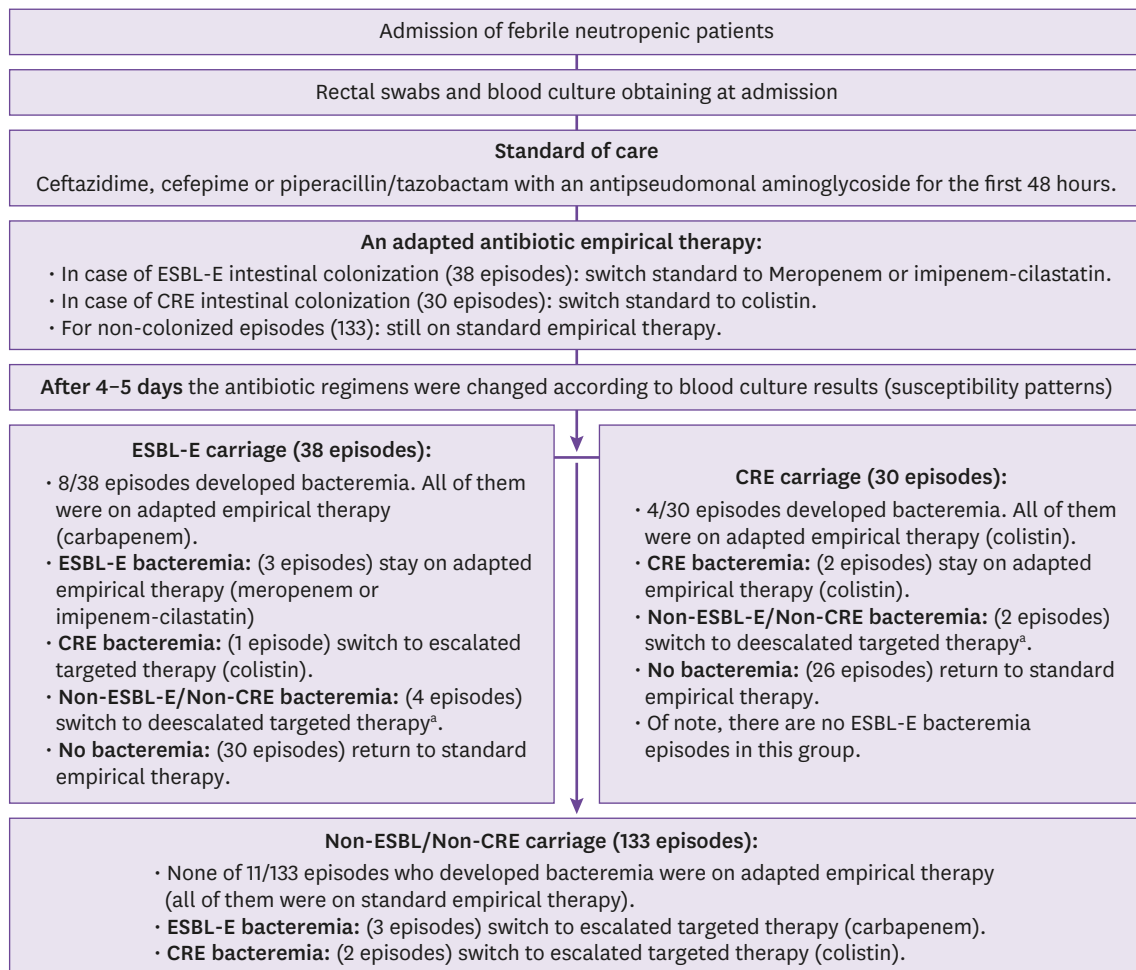

Figure 1. Flow diagram of treatment strategy according to ESBL-E and CRE colonization.
[a]According to *in vitro* susceptibility test report.
ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*.

Dickinson NMIC/ID-94 panels [13]. Baseline and demographic characteristics of colonized and non-colonized episodes were compared in order to assess risk factors for intestinal colonization by ESBL-E and CRE, and to assess the clinical outcomes of patients who underwent screening for intestinal colonization by MDR bacteria. Length of hospital stay, duration of antibiotic therapy, and 14-day and 28-day overall mortality rate were calculated.

2. Definitions

A febrile neutropenia episode was defined as a single oral temperature of ≥38.3°C or a temperature of ≥38.0°C (100.4°F) sustained over 1 hour with an absolute neutrophil count <500 cells/mm^3. Prior antibiotic therapy was defined as the administration of any systemic antibiotic within 1 month prior to admission [14]. ESBL-E or CRE colonization was defined as the detection of the respective organism in at least one rectal swab. BSI was defined as the detection of the causative pathogen in at least one blood culture. Standard empirical antibiotic therapy constituted the administration of an antibiotic (typically ceftazidime, cefepime, or piperacillin-tazobactam and amikacin) against suspected infection without prior identification of the causative pathogen according to our local institutional guidelines. Adapted empirical antibiotic therapy was defined as the administration of antibiotics according to rectal swab results. For example, if a rectal swab yielded ESBL-E or CRE pathogens, then carbapenem or colistin, respectively, were administered as empirical antibiotic therapy according to *in vitro* susceptibility reports. Escalated and deescalated targeted therapy referred to a standard or adapted antibiotic regimen which was escalated or deescalated to antibiotics, which exhibited documented *in vitro* activity against bloodstream isolates. For instance, if a rectal swab yielded non-ESBL/non-CRE pathogens, standard empirical antibiotic therapy was continued. Inadequate empirical antibiotic therapy was defined as the absence of treatment of bacteremia patients with at least one empirical antibiotic with proven *in vitro* activity against bloodstream isolates.

3. Statistical Analysis

BSI incidence and percentages of intestinal ESBLE and CRE carriers among enrolled patients were calculated. Chi-square test for categorical variables, Fisher's exact test for sample numbers less than 30, and Student's t-test for continuous variables were used to compare colonized and non-colonized episodes. Multivariate logistic regression analysis was performed to determine the risk factors associated with ESBL-E and CRE intestinal colonization based on the combination of ESBL-E and CRE colonized episodes as a single category versus the reference category (non-ESBL-E/non-CRE carriage). The mortality rate and adequacy of the prescribed treatment for patients who developed BSIs (ESBL-E and CRE colonized and non-colonized) were compared. Univariate logistic regression analysis was used for categorical variables. Non-ESBL-E/non-CRE carriage was set as the reference group for binary outcome (BSI, mortality), whereas non-ESBL-E/non-CRE bacteremia was set as the reference group for bacteremia outcome, which is a multinomial variable. A general linear model-univariate analysis of variance (ANOVA) was used to compare continuous variables among the three groups (ESBL-E, CRE, and non-ESBL-E/non-CRE carriage groups). Binary logistic regression analysis was performed in order to determine potential risk factors associated with mortality. Multivariate logistic regression analysis of factors potentially associated with ESBL-E/CRE acquisition and mortality included all statistically significant variables in univariate analysis as well as gender and age regardless of statistical significance. Variables close to significance (0.05 <*P* <0.1) were also included. IBM© SPSS© 20 (IBM SPSS Statistics, version 20; IBM, Armonk, NY, USA) was used for statistical analysis.

RESULTS

Throughout the course of the study, 201 rectal swabs and 402 blood culture specimens were obtained from 163 patients during 201 neutropenic fever episodes. Of 201 neutropenic fever episodes with rectal swab screening, 38 (18.90%) neutropenic fever episodes were identified to be colonized with ESBL-E and 30 (14.92%) with CRE. The demographic characteristics of the colonized patients are presented in **Table 1**. No statistically significant differences were observed between colonized and non-colonized groups in the majority of main baseline and demographic characteristics of all episodes. Previous quinolone administration was the only characteristic that demonstrated a significant difference between colonized and non-colonized episodes (92.1% in ESBL-E and 93.33% in CRE colonized episodes versus 45.86% in non-colonized episodes; P <0.0001). Prior quinolone use was an independent risk factor for ESBL-E and CRE colonization identified using an unconditional logistic regression model (odds ratio [OR], 17.09; 95% confidence interval [CI]s, 5.29 - 55.18; P <0.0001) (**Table 2**). The susceptibility rates of non-β-lactam antibiotic use among 38 ESBL-E isolates were as follows: trimethoprim-sulfamethoxazole, 42.1%; amikacin, 78.94%; gentamicin, 36.84%; tobramycin, 31.57%; and quinolones, 39.47%. Of the strains, 84.21% were susceptible to piperacillin-tazobactam, 63.15% to amoxicillin-clavulanic, and 57.89% to ampicillin-sulbactam. Of CRE strains, 16.66% were susceptible to trimethoprim-sulfamethoxazole, 36.66% to amikacin, and 83.33% to tigecycline. Bloodstream infections developed in 29/201 (14.42%) episodes. Only negative-rod BSIs were analyzed, which accounted for 23/201 (11.44%). The isolate distribution was as follows: negative bacilli, n = 23; coagulase-negative *Staphylococci*, n = 2; methicillin-sensitive *Staphylococcus aureus*, n = 1; and methicillin-resistant *S. aureus*, n = 3. Of note, isolates from rectal swab and blood sample cultures demonstrated similar antibiotic susceptibility patterns (ESBL-E or CRE resistance patterns) despite differences in strain.

Table 1. The demographic characteristics of colonized patients

Characteristics	Total	Colonized group		Non-colonized group	P-value[a]
		ESBL-E carriage	CRE carriage		
No. of episode (n, %)	201 (100)	38 (18.90)	30 (14.92)	133 (66.16)	-
Gender (male/female)	118/83	23/15	19/11	76/57	0.79
Mean age (years-range)	37 ± 13	36 ± 12	37 ± 11	38 ± 13	0.72
Diarrhea (n, %)	23 (11.44)	3 (7.89)	4 (13.33)	16 (12.03)	0.73
Prior hospitalization during previous month (n, %)	27 (13.43)	1 (2.63)	4 (13.33)	22 (16.54)	0.08
Previous neutropenic fever episode (n, %)	38 (18.90)	7 (18.42)	6 (20)	25 (18.79)	0.98
Underlying disease					
Acute leukemia (n, %)	171 (85.07)	31 (81.57)	22 (73.33)	118 (88.72)	0.19
Malignant lymphoma (n, %)	24 (11.94)	6 (15.78)	7 (23.33)	11 (8.27)	0.15
Myelodesplastic syndrome (n, %)	4 (1.99)	1 (2.63)	0	3 (2.25)	-
Myeloproliferative neoplasm (n, %)	2 (0.99)	0	1 (3.33)	1 (0.75)	-
Prior antibiotic therapy					
Cephalosporin (n, %)	167 (83.08)	33 (86.84)	24 (80)	110 (82.70)	0.74
Aminoglycosides (n, %)	172 (85.57)	32 (84.21)	26 (86.66)	115 (86.46)	0.95
Carbapenems (n, %)	52 (25.87)	11 (28.94)	7 (23.33)	34 (25.56)	0.86
Quinolones (n, %)	124 (61.69)	35 (92.10)	28 (93.33)	61 (45.86)	<0.0001
Penicillins (n, %)	44 (21.89)	8 (21.05)	7 (23.33)	30 (22.55)	0.97
Chemotherapy					
Anthracyclines (n, %)	181 (90.04)	34 (89.47)	27 (90)	120 (90.22)	0.91
Methotrexate (n, %)	56 (27.86)	10 (26.31)	8 (26.66)	39 (29.32)	0.95
Nitrogen mustard alkylating agents (n, %)	83 (41.29)	16 (42.10)	15 (50)	50 (37.59)	0.15
Pyrimidine analogue anti-metabolites (n, %)	135 (67.16)	24 (63.15)	19 (63.33)	91 (68.42)	0.82
Purine analogue anti-metabolites (n, %)	53 (26.36)	11 (28.94)	7 (23.33)	35 (26.31)	0.87

[a]P-value of this test demonstrates the significance of the difference between colonized and non-colonized episodes.
ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*.

Table 2. Independent risk factors for fecal extended-spectrum β-lactamase-producing *E. coli* and Carbapenem Resistant *Enterobacteriaceae*-carriage using unconditional logistic regression model

Risk factor	OR (95% CI)	*P*-value
Age	0.98 (0.96 – 1.01)	0.34
Gender (female)	1.33 (0.71 – 2.52)	0.37
Prior quinolone use	17.09 (5.29 – 55.18)	<0.0001
Prior hospitalization during previous month	0.48 (0.14 – 1.10)	0.07

OR, odds ratio; CI, confidence interval.

Intestinal colonization with ESBL-E or CRE exhibited a trend to be associated with the development of BSI with ESBL-E/CRE when compared to non-ESBL-E/non-CRE, but this did not reach statistical significance (OR, 1.56; 95% CI, 0.19 - 11.52; *P* = 0.69; and OR, 3; 95% CI, 0.28 - 37.67; *P* = 0.39; respectively) (**Table 3**). Of 38 ESBL-E colonized episodes, eight developed Gram negative-rod BSIs (three with ESBL-E, one with CRE, and four with non-ESBL-E/non-CRE isolates). Only three cases were continued on adapted empirical antibiotic therapy because their blood specimens also yielded ESBL-E. Two cases died due to septic shock and cerebral hemorrhage. The remaining bacteremia episodes included one with CRE who was switched to escalated targeted therapy (colistin) and four with non-ESBL-E/non-CRE who were switched to deescalated targeted therapy according to *in vitro* susceptibility test reports. In total, 30 non-bacteremic episodes were reverted to standard empirical therapy (**Fig. 1**).

Of 30 CRE carriage patients, four developed BSIs, two of which were caused by CRE isolates; these cases were maintained on adapted empirical therapy (colistin). One case in the adapted empirical antibiotic therapy group died within 14 days from the initiation of early treatment with colistin. Two of the CRE carriage episodes developed non-ESBL-E/non-CRE bacteremia; these episodes were subsequently treated with deescalated targeted therapy according to *in vitro* susceptibility results. The remaining 26 non-bacteremic episodes were reverted to standard empirical therapy (**Fig. 1**). Only one bacteremia patient in the non-colonized episodes group died within 14 days despite the lack of adapted empirical antibiotic therapy implemented in this population. As shown in **Table 3**, no significant differences were observed in duration of hospitalization between ESBL-E, CRE, and non-ESBL-E/non-CRE carriage episodes (*P* = 0.72), or in duration of antibiotic therapy between ESBL-E, CRE, and non-ESBL-E/non-CRE carriage episodes (*P* = 0.84). The 14-day mortality rate for ESBL-E and CRE-colonized episodes was higher than that for non-colonized episodes (7.89%, 3.33%, and 0.75%; respectively) (**Table 4**). The 14-day mortality for ESBL-E carriage episodes was significantly higher than that for non-colonized episodes (OR, 11.31; 95% CI, 1.14 – 112.13; *P* = 0.03). No significant difference in 14-day mortality was observed between

Table 3. Univariate analysis of outcomes according to the extended-spectrum β-lactamase/carbapenem resistant *Enterobacteriaceae* fecal carriage

Categorical outcome	ESBL-E carriage *P*, OR (95% CI)	CRE carriage *P*, OR (95% CI)	Reference group
BSI episodes[a]	0.11, 2.95 (0.89 – 7.59)	0.39, 1.72 (0.56 – 5.78)	Non-ESBL-E/Non-CRE carriage
ESBL-E bacteremia[a]	0.69, 1.56 (0.19 – 11.52)	NA	Non-ESBL-E/Non-CRE bacteremic episodes
CRE bacteremia[a]	0.83, 0.75 (0.05 – 11.31)	0.39, 3 (0.28 – 37.67)	Non-ESBL-E/Non-CRE bacteremic episodes
Total deaths within 14 days[a]	0.03, 11.31 (1.14 – 112.13)	0.28, 4.55 (0.27 – 74.91)	Non-ESBL-E/Non-CRE carriage
28-day overall mortality[a]	0.68. 1.25 (0.41 – 3.82)	0.79, 1.21 (0.34 – 4.26)	Non-ESBL-E/Non-CRE carriage
Continuous outcome	(ESBL-E, CRE, Non-ESBL-E/Non-CRE) carriage		
Days of hospitalization[b]	*P* = 0.72		
Days of antibiotic therapy[b]	*P* = 0.84		

[a]Univariate logistic regression for categorical outcome. [b]General linear model/univariate analysis of variance for continuous outcome between three categories of carriage.
ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds ratio; CI, confidence interval; NA, not applicable.

Table 4. Outcomes of the study population according to the extended-spectrum β-lactamase/carbapenem resistant *Enterobacteriaceae* fecal carriage

Characteristics	ESBL-E carriage	CRE carriage	Non-ESBL-E/Non-CRE carriage
Number of episode which developed gram negative rods BSI (n/N, %)	8/38 (21)	4/30 (13.33)	11/133 (8.27)
ESBL-E bacteremia (n/N, %)	3/38 (7.89)	0	3/133 (2.25)
CRE bacteremia (n/N, %)	1/38 (2.63)	2/30 (6.66)	2/133 (1.50)
Non-ESBL-E/Non-CRE bacteremia (n/N, %)	4/38 (10.52)	2/30 (6.66)	6/133 (4.51)
Treatment			
Standard-of-care (n/N, %)	30/38 (78.94)	26/30 (86.66)	133/133 (100)
Adapted empirical (n/N, %)	8/38 (21)	4/30 (13.33)	-
Deescalated targeted (n/N, %)	4/38 (10.52)	2/30 (6.66)	-
Escalated targeted	1/38 (2.63)	0	5/133 (3.75)
Inadequate empirical	0	0	5/133 (3.75)
Days of hospitalization (mean ± SD)	23.34 ± 5.7	22.94 ± 5.4	22.42 ± 5.21
Days of antibiotic therapy (mean ± SD)	19.65 ± 4.19	19.25 ± 3.99	19.18 ± 3.79
14-day mortality among ESBL-E bacteremia (n/N, %)	2 (5.26)	-	0
14-day mortality among CRE bacteremia (n/N, %)	0	1/30 (3.33)	0
14-day mortality among Non-ESBL-E/Non-CRE bacteremia (n/N, %)	1/38 (2.63)	0	1/133 (0.75)
Total deaths within 14 days (n/N, %)	3/38 (7.89)	1/30 (3.33)	1/133 (0.75)
28-day overall mortality (n/N, %)	4/38 (10.52)	3/30 (10.00)	11/133 (8.27)

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*; SD, standard deviation.

Table 5. Multivariate binary logistic regression for 28-day overall mortality

Risk factor	OR (95% CI)	*P*-value
Age	1.02 (0.98 – 1.06)	0.82
Gender	0.99 (0.95 – 1.03)	0.94
ESBL-E carriage	1.30 (0.39 – 4.35)	0.66
CRE carriage	1.23 (0.32 – 4.72)	0.76

Reference category: Non-ESBL-E/Non-CRE carriage.
OR, odds ratio; CI, confidence interval; ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*.

CRE carriage episodes and non-colonized episodes (OR, 4.55; 95% CI, 0.27 - 74.91; *P* = 0.28) (**Table 3**). No significant differences in 28-day mortality rate were observed between ESBL-E carriage episodes and non-colonized episodes (OR, 1.25; 95% CI, 0.41 - 3.82; *P* = 0.68) or between CRE carriage episodes and non-colonized episodes (OR, 1.21; 95% CI, 0.34 - 4.26; *P* = 0.79) (**Table 3**). Binary logistic regression analysis revealed no significant differences between ESBL-E or CRE-colonized episodes and non-colonized episodes (OR, 1.30; 95% CI, 0.39 - 4.35; *P* = 0.66 and OR, 1.23; 95% CI, 0.32 - 4.72; *P* = 0.76; respectively) (**Table 5**). The outcomes of the study population according to the extended-spectrum β-lactamase/carbapenem-resistant *Enterobacteriaceae* fecal carriages are presented in **Tables 3**, **4**, and **5**.

DISCUSSION

Our study aimed to test the efficacy of a new locally applied protocol based on modifications to empirical antibiotic therapy. The adapted therapy aimed to reduce bacteremia-related mortality among patients with febrile neutropenia. The ESBL-E intestinal colonization rate was estimated to be 18.9% in the present study, which was similar to the colonization rate reported by Liss et al. (17.5%) [7]. Another study reported a lower colonization rate (11.1%) [15], whereas Arnan et al. reported a higher rate of 31.8% [16].

In our study, 14.9% of the included episodes were CRE-colonized. A similar rate was reported by Demiraslan et al. (11.4%) [8], whereas a higher rate of CRE colonization (24.4%) was

reported by Christophy et al. [17]. The ESBL-E/CRE intestinal colonization rate in our study is comparable to that of the Syrian population [10-12]. Various causes may underpin this high rate of colonization by MDR bacteria, such as ineffective infection control measures in Syrian health care facilities, the absence of antibiotic stewardship programs, and massive population displacement and temporary sheltering due to war. No significant differences were observed in baseline characteristics or clinical features between ESBL-E/CRE-colonized and non-colonized patients. Previous quinolone exposure was the only variable identified as an independent risk factor for ESBL-E/CRE colonization. This is consistent with previous reports which concluded that previous antibiotic use, especially quinolone, was a risk factor for ESBL-E and CRE colonization [7, 16, 18, 19]. In our two centers, prophylactic use of quinolone for neutropenic patients is indicated for high-risk neutropenic patients (patients anticipated to have an absolute neutrophil count [ANC] <500 cells/mm^3 for >7 days) [20]. As such, the extensive use of quinolone in this population may underscore this observation. In contrast, depending on previous hospitalization and history of febrile neutropenia episodes, hospital admissions were not identified as risk factors for intestinal colonization by MDR bacteria. This finding is suggestive of community-acquired MDR bacteria due to the aforementioned circumstances. Poultry have been identified as a potential reservoir of bacteria [21]. Moreover, using thermal inactivation to kill food contaminants and hygienic precautions between chemotherapy cycles may reduce colonization by MDR pathogens [22].

Of 38 ESBL-E fecal carriage episodes, eight (21%) developed BSI, and only three (7.9%) bacteremia episodes were due to ESBL-E. A similar ratio (6.6%) was reported by Liss et al [7]. As noted previously, fecal carriage of ESBL-E does not significantly contribute to the etiology of subsequently developed BSI (*P* >0.05), as shown in **Table 3**. Arnan et al. reported that the rates of BSIs with non-ESBL-E in ESBL-E fecal carriage and BSIs with ESBL-E were 10% and less than 2%, respectively, in the same group [16]. Intestinal colonization with ESBL-E has been reported to increase the risk of ESBL-E infections in febrile neutropenic patients [7, 15, 23]. When examining BSIs in four (13.3%) of 30 CRE-colonized episodes, we observed two cases of CRE-caused bacteremia. Similar rates have been reported in previous studies [18, 24]. One study reported that 21.2% of CRE-colonized episodes developed a BSI with CRE [25]. In our study, no significant association was observed between intestinal colonization by ESBL-E/CRE and increased BSIs by bacteria expressing the same resistance mechanism (**Table 3**). This finding could be due to low detection sensitivity resulting from a scarcity of documented infections and the inability of our culture-based protocol to detect cases of low-level colonization on admission. Nevertheless, colonization may reach high levels due to an increase in bacterial burden and the selective pressure exerted by empirical antimicrobial therapy for febrile neutropenia following admission. Indeed, colonization is a dynamic process, and more than one swab culture must be obtained in order to estimate the exact time of colonization. Therefore, it is important to perform two rectal swabs at 2-week intervals in order to precisely determine the absence of colonized episodes. Based on these factors, the rate of intestinal colonization by ESBL-E/CRE may have been underestimated in our study.

Of 38 ESBL-E-colonized episodes that developed BSIs, eight received adapted empirical antibiotic therapy with carbapenems. Blood specimens of three of these patients yielded ESBL-E. Two of these patients died despite early carbapenem therapy before blood culture results were obtained. In total, 30 CRE-colonized episodes were treated with colistin as adapted empirical antibiotic therapy. Two patients developed CRE BSI and were continued on colistin; one of these patients died due to septic shock. The lowest mortality rate was documented in the non-colonized group, which did not receive adapted empirical antibiotic therapy.

Liss et al. reported good prognosis and reduced mortality rates among ESBL-E-carrying patients when an adapted empirical antibiotic therapy was administered, although the causal factors driving the reduction in mortality were unclear [7]. Accordingly, a causal relationship between the implementation of rectal swab screening-based adapted empirical antibiotic therapy and reduced mortality rate cannot be definitively established. Moreover, no significant between-group differences were identified in the duration of hospitalization and administered course of antibiotics.

Our study has several limitations. We did not screen the lower urinary tract for bacterial colonization. Hence, urine samples were not included in our protocol. Thus, our study may have underestimated the true rate of ESBL-E/CRE colonization. In order to identify non-carrier patients, two consecutive rectal swabs negative for ESBL-E/CRE must be documented. Due to our resource-limited setting in a war-torn health system, we were unable to ensure that more than one swab was obtained for each patient. Moreover, a proportion of colonized patients may have had low-level colonization which impeded detection in the first swab. Further, we did not perform pulsed-field gel electrophoresis which would have facilitated molecular characterization at the subspecies level to obtain more reliable data on bacterial translocation from the intestine to the bloodstream. We relied upon biochemical identification and susceptibility testing in order to compare isolates. Additionally, the sample size of ESBL-E/CRE bacteremia episodes was small, which may have precluded the detection of statistically significant differences between groups.

In conclusion, intestinal colonization by ESBL-E and CRE was not significantly associated with subsequent BSIs caused by bacteria expressing the same resistance mechanisms. Although further confirmation is required, early adapted empirical antibiotic therapy based on colonization status demonstrated limited benefits in this specific setting.

ACKNOWLEDGMENT

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